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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,571	CALAS ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-25,29,30 and 32-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-25,29,30 and 32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 18-25, 29, 30 and 32-36 are pending.

Applicants' amendment filed December 4, 2003 is acknowledged, and applicants' response has been fully considered. Claims 21, 29, 35 and 36 have been amended, and claim 31 has been cancelled. Thus, claims 18-25, 29, 30 and 32-36 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

2. The previous rejection of claim 31 and 36, under 35 U.S.C.112, first paragraph, is withdrawn in view of applicants' cancellation of the claim, and applicants' amendment to the claim in the amendment filed December 4, 2003.

3. The previous rejection of claim 21, 31 and 35, under 35 U.S.C.112, second paragraph, regarding SEQ ID NO:11 or 12 and antecedent basis, is withdrawn in view of applicants' cancellation of the claim, and applicants' amendment to the claim, and applicants' response at page 9 of the amendment filed December 4, 2003.

Claim Objections

4. Claim 23 is objected to because of the use of "(VI(SEQ ID NO:14)" in line 6.

Objection to New Matter Added to Specification

5. The amendment filed December 4, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The specification does not indicate a

compound of the formula (IV) having $(YAZ)_m$, however, claim 25 in the amendment recites the new matters.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 18-25, 29, 30 and 32-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a linear peptide SEQ ID NO:23 obtained from an antibiotic peptide; a specific compound of formula (IV), wherein A is the peptide sequence indicated in Tables I and II and encompassed by SEQ ID NO:13 or 14, Z is biotin or doxorubicin, m=1 and n=0; or a method of vectoring biotin or doxorubicin to a target cell using the conjugate of biotin-peptide or doxorubicin-peptide, wherein the peptide is indicated in Tables I and II, does not reasonably provide enablement for an analog of SEQ ID NO:23 obtained from an antibiotic peptide, where the sequence of the analog is not defined; a compound of formula (IV), wherein the amino acid residues in SEQ ID NO:11, 12, 13 or 14 of A, Z and Y are not specifically defined; a pharmaceutical composition comprising the compound of formula (IV); a diagnostic agent comprising the compound of formula (IV); or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide from β-stranded antibiotic peptides or analogs thereof, wherein the linear peptide, the active substance, the signal agent and the target cell, cell compartment, or organ are not specifically defined. The specification does not enable a person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 18-25, 29, 30 and 32-36 encompass a linear peptide SEQ ID NO:23 obtained from an antibiotic peptide or an analog thereof (claims 18, 19, 35 and 36); a compound of formula (IV) (claims 25, 29, 30, 32); a pharmaceutical composition comprising the compound of formula (IV) (claim 33); a diagnostic agent comprising the compound of formula (IV) (claim 34); or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide from β-stranded antibiotic peptides or analogs thereof (claims 20-24). The specification, however, only discloses cursory conclusions (page 8, line 19-page 13, line 7) without data supporting the findings, which state that the peptide derived from an antibiotic peptide having the formula (I) or (II), or moieties of the peptides, and a compound of formula (IV) containing the peptide, an active substance and a signal agent, can be used to vector one or more active substances for therapeutic and for diagnostic applications. There are no indicia that the present application enables the full scope in view of the compound of formula (IV) and the peptides obtained from β-stranded antibiotic peptides, and the method vectoring an active substance using the peptide as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the

art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the analogs of SEQ ID NO:23; the linear peptide and the active substance in the conjugate; and the linear peptide, the active substance and the signal agent in compounds of formula (IV), which are not adequately described or demonstrated in the specification.

(2). The presence of working examples:

The specification only demonstrates specific analogs of protegrin and tachyplesin (Tables I and II), which do not have disulfide bond; the conjugates of the peptide with doxorubicin or biotin; and the internalization abilities of these peptides in different cell lines, which was the basis for vectoring an active substance in an organism (Examples 1-4). However, there are no other working examples indicating the claimed variants or methods in association with the variants.

(3). The state of the prior art and relative skill of those in the art:

The related art has shown certain analogs of protegrin and tachyplesin (e.g., pages 20-22 in Lehrer *et al.* WO 96/37508), which do not have cysteines and have decreased antimicrobial activity as compared to peptides having disulfide bonds. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of various analogs of SEQ ID NO:23, various linear peptides and the active substance in the conjugate, and the signal agent in the compound of

formula (IV), and the effect of the conjugate in vectoring an active substance to be considered enabling for all variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a linear peptide of SEQ ID NO:23 or analogs thereof, a compound of formula (IV), a pharmaceutical composition or a diagnostic agent comprising the compound of formula (IV), or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide from β-stranded antibiotic peptides or analogs thereof. The specification only indicates certain analogs of protegrin and tachyplesin (Tables I and II) and the conjugates of the peptide with doxorubicin or biotin, it also shows the internalization abilities of these peptides in different cell lines, which was the basis for vectoring an active substance in an organism (Examples 1-4). However, the specification fails to identify various analogs of SEQ ID NO:23, various compounds of formula (IV) containing a peptide from β-stranded antibiotic peptides, an active substance and a signal agent, and various conjugates containing a β-stranded antibiotic peptide and an active substance, nor demonstrates the effects of analogs of SEQ ID NO:23 or the conjugates in vectoring active substances to specific cell compartments, cells or organs. Moreover, the specification has not shown the conjugates containing various β-stranded antibiotic peptides can internalize into the cell to vector various active substances in an organism. There are no working examples indicating the claimed variants and associated methods except for the conjugate of biotin-peptide or doxorubicin-peptide containing a specific antibiotic peptide sequence. Furthermore, the specification does not provide any specific

guidance on the identities of various analogs of SEQ ID NO:23, various peptides obtained from other β-stranded antibiotic peptides such as defensins or polyphemusins, the effects of the conjugates in vectoring an active substance, and how to make/use the pharmaceutical composition with the conjugate, or how to use the conjugate as the diagnostic agent. Since the specification fails to provide sufficient teachings on the identities of various analogs of SEQ ID NO:23, various peptides from β-stranded antibiotic peptides, various actives substances, and various signal agents, and the effects of the conjugates, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the linear peptides in vectoring active substances to target cells.

(5). Predictability or unpredictability of the art:

As indicated in the previous sections, there are only limited peptides identified as the analogs of β-stranded antibiotic peptides. Because the amino acid sequences of SEQ ID NO:23 analogs, peptides of formulas (I) or (II), and peptides obtained from other antibiotic peptides are highly variable, it is not known whether these peptides would have an internalization ability as the peptides shown in Table III and IV. The claims encompass many variants and the outcome of the claimed method is highly unpredictable, and for the peptide listed in the table it is not readily apparent that one would have been able to a priori predict the degree of internalization ability of each peptide and the effect of the conjugate.

(6). Nature of the Invention

The scope of the claims includes many structural variants, but the specification has not shown various linear peptides or peptide analogs can internalize into various cells, nor has

demonstrated the effects of the linear peptides in vectoring various active substances. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the guidance and the teaching in the specification are limited, the effect of the claimed compound is unpredictable, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the claimed variants in vectoring an active substance.

In response, applicants indicate the present invention discloses compounds of formula (IV) and compositions which use the compounds to vector active ingredients in cells or organs; the specification discloses examples of peptides from protegrin and tachyplesin, and the peptide internalization properties are shown in Example 3, as a consequence, one skilled in the art can use the teaching of the test compounds for other peptides of general formula (I), (II), (V) or (VI); Example 4 discloses the internalization of doxorubicin vectored because of the claimed peptide, SM1738; the specification describes biotin and doxorubicin as active substance, several kinds of signal agents, the peptides and compounds of formula (IV), and one skilled in the art knows the active ingredients which can be used to treat any pathology affecting humans or animals, knows several examples of signal agents which can be used to vector the compound of formula (IV) to a particular cell type, a particular cell compartment or a particular organ (pages 8- 9 of the response). The response has been fully considered, however, the argument is not found persuasive because the specification only shows internalization abilities of specific analogs of protegrin and tachyplesin (Tables I and II) in different cell lines (Example 3) and the internalization of the conjugate of SM 1738 and doxorubicin (Example 4), it has not

demonstrated a compound of formula (IV) containing a linear peptide from β-stranded antibiotic peptide, an active substance and a signal agent is effective in vectoring a specific active substance to a specific cell compartment, cell or organ, nor has shown the conjugates containing various linear peptides from β-stranded antibiotic peptides (e.g., defensins or polyphemusins) and various active substances have been vectored to a specific target cell, cell compartment or organ, which are encompassed by the claims. Thus the full scope of the claim is not enabled as indicated in the section above.

7. Claims 25, 30 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 25, 30 and 32-34 are directed to a compound of the formula (IV): $(YAZ)_m$, where A is a linear peptide obtained from a β-stranded antibiotic peptide having the formula (I), (II), (V) or (VI), Z is an active substance, Y is a signal agent, n is 0 or 1, and m is 1-10. The specification indicates the instant invention provides a compound of the formula (IV): $(Y)_n$-(A)-$(Z)_m$, where A is a linear peptide obtained from a β-stranded antibiotic peptide, Z is an active substance, Y is a signal agent, n is 0 or 1, and m is 1-10, it does not indicate a compound of the formula (IV) is $(YAZ)_m$. There is no example demonstrating the make /use of the compound of the formula (IV): $(YAZ)_m$ and the effect of the compound in targeting to the particular cell or organ. The lack of structure/activity and the lack of representative species for the compound of the formula (IV): $(YAZ)_m$ as encompassed by the claims, applicants have failed to sufficiently

describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 18-25, 29, 30, 32-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 18, 19, 35 and 36 are indefinite because of the use of the term "An isolated linear peptide obtained from an antibiotic peptide or an analog thereof". The term renders the claim indefinite, is not clear to what peptide the analog is referred, e.g., is it the analog of an isolated linear peptide, or of an antibiotic peptide? Claims 19, 35 and 36 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

10. Claims 20-25, 29, 30 and 32-34 are indefinite because of the use of the term "chemical molecules for the treatment or prevention of human or animal pathologies", "a particular cell compartment, a particular cell type or a particular organ" or "said signal agent having an affinity towards a particular cell type, cell compartment or a specific tissue or organ, or the ability to recognize a specific determinant present on a particular cell type, cell compartment or a specific tissue or organ". The term cited above renders the claim indefinite, is not clear what structure the chemical molecule has, and what disease state is as to "the human or animal pathology"; which cell compartment, cell type, tissue or organ is as to "a particular cell compartment, a

particular cell type or a particular organ" or "a particular cell type, cell compartment or a specific tissue or organ, what the determinant is; and how the active substance coupled with the peptide can target at a particular cell compartment, a particular cell type or a specific tissue or organ without identifying the cell compartment, cell type, tissue or organ. Claims 21-24, 30 and 32-34 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

In response, applicants indicate the present invention discloses biotin and doxorubicin as active substance, one of skilled in the art knows different kinds of active substances can be used according to the present invention; the specification describes several kinds of signal agents, the peptides and compounds of formula (IV), and one skilled in the art knows the active ingredients which can be used to treat any pathology affecting humans or animals, knows several examples of signal agents which can be sued to vector the compound of formula (IV) to a particular cell type, a particular cell compartment or a particular organ (page 9 of the response). The response has been fully considered, however, the argument is not found persuasive because the particular cell type, cell compartment or a tissue or organ, and the determinant on the cell type as well as the signal agent have not been identified in the claim, thus it is not clear what is the target cell or organ for the signal agent, and how the signal agent would recognize the target cell or organ without identifying of the determinant.

11. Claim 25 recites the limitation "n is 0 or 1" in line 43. There is insufficient antecedent basis for this limitation in the claim because there is no "n" in formula (IV).

12. Claim 29 recites the limitation "A" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 29 is also indefinite as to formula (IV), it is not clear what formula (IV) is.

13. Claim 36 recites the limitation "tachyplesins" in line 3. There is insufficient antecedent basis for this limitation in the claim because claim 19 recite the peptide having SEQ ID NO:23, which is the peptide analog of protegrins not a peptide analog of tachyplesins.

Conclusions

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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February 28, 2004

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